Amendments to the Specification

Please replace the paragraph after RELATED APPLICATIONS (see Amendment dated October 10, 2003) at page 1, lines 3 through 14, with the following amended paragraph:

BACKGROUND OF THE INVENTION ~~DESCRIPTION~~

The present invention relates to nucleic acids that have a modified expression caused by hyperplasias and/or tumours, nucleic acids coding for the human homologues to CAT, DC2, hereinafter also called CAT and DC2, and PKCgamma and especially homologues thereof, containing vectors and cells containing these, polypeptides encoded by these, antibodies directed there towards, methods for determining compounds suitable as therapeutic substances for tumours, methods for determining genes involved in the formation of tumours of the thyroid gland and uses of said nucleic acids.

Please replace the paragraph at page 2, lines 10 through 18 with the following amended paragraph:

SUMMARY OF THE INVENTION

The object of the present invention is to provide means for the diagnosis and treatment of functional disorders of the thyroid, hyperplasias of the thyroid and tumours of the thyroid on the molecular level, especially to provide nucleic acid sequences which are involved in the pathogenicity mechanisms and are also suitable for investigating these mechanisms, as well as those which act on the pathogenicity mechanisms or can influence these mechanisms.

Please insert the following new text after the paragraph at page 15, lines 21 through 25:

--BRIEF DESCRIPTION OF THE DRAWINGS

The invention is explained below with reference to the drawings and examples as well as the sequence protocol from which further features, embodiments and advantages of the invention are obtained. ~~In the figures:~~

FIG. 1 is a metaphase of the cell line S 141.2 with t(2;19)(p12;q13) after G-banding wherein the chromosomes 19, der(19) and der(2) are marked with an arrow (a); FIG. 1(b) is the same metaphase after FISH with the BAC clone 280723 (the hybridisation signals are localised on the chromosomes 19, der(19) and der(2).

FIG. 2 is a schematic diagram of the break point cluster region in benign thyroid tumours with 19q13 aberrations. The FISH mapping data of the six tumours tested in the trial show that the break points of the benign thyroid tumours with 19q13 translocations in the region around 150 kbp 3' map to RITA. The cosmid, BAC and PAC clones agree with the physical map of chromosome 19 of the Lawrence Livermore National Laboratory. The encircled numbers refer to the newly established STS marker RSTS1-RSTS 10 (for comparison see Table 2);

FIG. 3 shows the results of a Northern Blot hybridisation on RNA isolated from thyroid adenoma cell line S121/SV40 and fibroblasts, using a 1092 bp cDNA probe of exon 1 to exon 5. The 5.5 kb and 6.2 kb transcripts were found in the fibroblasts and the adenoma cell line; and

FIG. 4 shows the genome position of the CAT-A gene;

FIG. 5 shows the genome organisation of CAT-A;

FIG. 6 is an organisational sketch of the mRNA of CAT-A;

FIG. 7 shows the various open reading frames as well as open reading frames with possible amino acid sequences designated herein as ORFstart1, ORFstart2 and ORF3;

FIG. 8 shows the position of the PKCG gene;

FIG. 9 is a Northern Blot to detect PKCG on thyroid carcinoma cells and thyroid normal tissue;
FIG. 10 is the result of a semiquantitative RT-PCR of the PKCG gene;

FIG. 11 is a diagram of the various genes or gene part sequences described herein for the first time relating to CAT-A or CAT-A1, the DC-2 homologue and protein kinase Cgamma;

FIG. 12 shows the result of a transmembrane domain analysis using the DAS program of the gene product of ORFstart1;

FIG. 13 shows the result of a transmembrane domain analysis using the DAS program of the gene product of ORFstart2;

FIG. 14 shows the result of a transmembrane domain analysis using the DAS program of the gene product of ORF3;

FIG. 15 shows the cDNA of CAT-A;

FIG. 16 shows the protein or amino acid sequence of ORFstart1 of CAT-A-cDNA;

FIG. 17 shows the protein or amino acid sequence of ORFstart2 of CAT-A-cDNA;

FIG. 18 shows the protein or amino acid sequence of ORF3 of CAT-A-cDNA;

FIG. 19 shows the cDNA of CAT-A1;

FIG. 20 shows the genome organisation or sequence of CAT-A or CAT-A1 with more extensive sequence information;

FIG. 21 shows the cDNA of CAT-A with more extensive sequence information;

FIG. 22 shows the genome sequence of the DC2 homologous gene according to the invention;

FIG. 23 shows the genome sequence of the DC2 homologous gene according to the invention with more extensive sequence information;

FIG. 24 shows the cDNA off the DC2 homologous gene with more extensive sequence information;

FIG. 25 shows the cDNA of PKCG with more extensive sequence information; and

FIG. 26 shows the genome sequence of PKCG with more extensive sequence information.--

Please replace the paragraph at page 70, lines 1 through 6, with the following amended paragraph:

~~CLAIMS~~

CLAIMS

We claim:

1. A nucleic acid that has a modified expression in hyperplasias and/or tumours, characterised in that it comprises a nucleic acid sequence which is selected from the group comprising SEQ. ID. No. 1, 2, 7, 10, 11 and 12.

Please replace the paragraph at page 15, lines 3 through 34, with the following amended paragraph:

DETAILED DESCRIPTION

The present invention is based on the surprising finding that there are a series of genes or nucleic acid sequences whose modified expression compared with normal tissue can be suspected of being connected with the occurrence of tumours and hyperplasias and appears to be causally connected thereto.

Please replace the paragraph at page 57, lines 9 through 23, with the following amended paragraph:

The cDNA or mRNA sequences of the afore-mentioned ESTs were checked for expression in a Virtual Northern (SAGE, serial analysis of gene expression; at the world wide web (www) ncbi.nlm.nih.gov/SAGE/ ~~http://www.ncbi.nlm.nih.gov/SAGE/~~). During this online analysis selected sequences of ESTs (tags) were compared with the sequences ordered in libraries. Although these results rather represent the frequency of the tag and less the actual gene expression, it is however a reliable instrument for first evaluations. Tags of the ESTs BE271492 and AF201937 (DC2) are found in many libraries, and particularly strong "expression" is found in libraries of medulloblastomas, mamma-adenocarcinomas, normal vascular endothelium cell lines, normal skin and prostatic carcinomas. Tags of the ESTs AF345987 and X62533 (PKCgamma) were only found in two libraries produced from normal brain or astrocytoma cell lines. Tags of the ESTs BE564764 and BF029168 could not be found in the libraries.

Please replace the paragraph at page 62, lines 28 through 35 and page 63, lines 1 through 2, with the following amended paragraph:

Possible transmembrane domains of the different reading frames were determined using a total of three different software programs. The corresponding software programs are "DAS" Transmembrane Prediction can be found at the www site, sbc.su.se/~miklos/DAS/ ~~which can be downloaded via the following URL address: http://www.sbc.su.se/~miklos/DAS/~~. This method was developed by Cserzo et al. (M. Cserzo, E. Wallin, I. Simon, G. von Heijne and A Elofsson: Prediction of transmembrane alpha-helices in procariotic membrane proteins: the Dense Alignment Surface method: Prot. Eng. vol. 10, no. 6, 673-676, 1997).

Please replace the paragraph at page 63, lines 7 through 16, with the following amended paragraph:

Another method for determining transmembrane domains is provided by the so-called HMMTOP server. HMMTOP is an automatic server for the prediction of transmembrane helices and topologies of proteins as developed by G. E. Tusnády from the Institute of Enzymology. The corresponding www site ~~URL address~~ is: enzim.hu/hmmtop/index.html ~~http://www.enzim.hu/hmmtop/index.html~~. The method is also described in Tusnády, G. E. et al. (G. E. Tusnády and I. Simon (1998) Principles Governing Amino Acid Composition of Integral Membrane Proteins: Applications to Topology Prediction. J. Mol. Biol. 283, 489-506).

Please replace the paragraph at page 63, lines 24 through 32, with the following amended paragraph:

Another method for predicting transmembrane regions is the so-called TMpred program. The algorithm is based on a statistical analysis of TMbase, a database of naturally occurring transmembrane proteins. The prediction is made using a combination of a plurality of weighted matrices. The corresponding www ~~URL address~~ is: ch.embnet.org/software/TMPRED form.html ~~www.ch.embnet.org/software/TMPRED form.html~~. The method is also described by Hofmann et al. (K. Hofmann & W. Stoffel (1993) TMbase - A database of membrane spanning protein segments Biol. Chem. Hoppe-Seyler 374, 166).